IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		Docket No.:	4258-113
Applicants:	SILVA GUISASOLA, Luis Octavio, et al.	Conf. No.:	8347
Application No.:	10/542,821	Art Unit:	1612
Date Filed:	July 20, 2005	Examiner:	Barbara P. Badio
Title:	PROCESS FOR OBTAINING 17α-ACETOXY-11β-(4-N,N-DIMETHYLAMINOPHENYL)-19-NORPREGNA-4,9-DIENE-3,20-DIONE	Customer No.:	23448

DECLARATION UNDER 37 CFR §1.132 IN U.S. PATENT APPLICATION NO. 10/542,821

VIA EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Antonio Lorente Bonde-Larsen hereby declares:

1. THAT I am a Spanish citizen, residing at Arribes del Duero 9, E-47151, Boecillo (Valladolid), Spain. I graduated in the University Autonoma of Madrid in Chemistry in 1988. After working in an Organic Chemistry Laboratory for three years, I carried out postgraduate research with Professor José Luis García Ruano in the Organic

Chemistry Laboratory at the same University, leading to the award of Doctor in Chemistry in 1997. From March 1994 until the present I have been employed by Ragactives (nowadays Gadea Group which includes Ragactives and Crystal Pharma). I worked initially as a Senior Research Scientist, and I have been working as Research and Development Manager since 2008.

2. THAT I have worked in the synthesis of different pharmaceutical active ingredients, wherein my research and development work has covered a range of different analytical techniques including for example high performance liquid chromatography (HPLC), gas chromatography (GC) as well as identification techniques including nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC), X-ray difraction, infrared (IR) spectroscopy, etc. I have also analyzed final pharmaceutical products and evaluated the quality and the impurities associated to them.

3. THAT I have read and am familiar with U.S. patent application No. 10/542,821 and with the U.S. Patent Final Office Action dated June 9, 2010 concerning the subject application. In fact, I prepared a Declaration dated March 3, 2010 in support of the patentability of the claims of said US patent application in response to a former Office Action dated November 4, 2009, wherein the Examiner rejected claims 1-8, 10, 12-14, 16-17, 19-22 and 24-26 under 35 U.S.C. 103 as purportedly being obvious over a combination of PCT WO 96/30390 by Kim ("Kim") and PCT WO 99/45022 by Cook et al. ("Cook"). Copy of my *curriculum vitae* ("CV") was provided as an attachment 2 to said declaration.

4. THAT I am aware that in said Final Office Action (FOA) dated June 9, 2010, it is stated that:

> *"(a) a purity of 99.2% is not considered significantly different from that of 98.57%"* [FOA, page 4, second paragraph, lines 4-5];
>
> *"Because VA-2914 have a medicinal use further purification would be prima facie obvious"* [FOA, page 4, second paragraph, lines 7-8]; and

"(b) a melting point of "around" 189°C would fall within the range of 183-185°C taught by Cook" [FOA, page 4, second paragraph, lines 4-5].

5. THAT one of the purposes of this Declaration is related to point out what are the levels of quality required by the Pharmaceutical Industry in relation with the active pharmaceutical ingredients (APIs) obtained for commercial use and the importance of the relative amount of each impurity present together with the API; another purpose of this Declaration is to point out my experience in relation with additional purifications following the process described by Kim; and another purpose of this Declaration is to discuss on the reliability of the differential scanning calorimetry technique for measuring the melting point of a compound.

6. THAT with respect to the statement *"(a) a purity of 99.2% is not considered significantly different from that of 98.57%"*, it is worth mentioning, before discussing this issue, as a general introduction, some comments concerning impurities present together with the API (i.e., the quality level required by the Pharmaceutical Industry in relation with the APIs obtained for commercial use) and the importance of the relative amount of each impurity present together with the API.

Concerning impurities present together with an API

A. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

B. ICH Harmonized Tripartite Guideline / Impurities in New Drug Substances Q3A, enclosed herewith as Annex 1, is the ICH's Guideline in relation to the acceptance criteria for the impurities present together with the API.

C. As an annex to the ICH guidance for industry, both the European Medicine Agency (EMEA) and the U.S. Department of Health and Human Service, Food and Drug Administration (FDA) have introduced in addition a guidance regarding the Safety Qualification of Impurities with known or suspected genotoxic or carcinogenic potential, namely

> "European Medicines Agency EMEA/CHMP/QWP/251344/2006, Guideline on the Limits of Genotoxic Impurities", enclosed herewith as Annex 2, and
>
> "U.S. Department of Health and Human Services /Food and Drug Administration /Center for Drug Evaluation and Research (CDER) /December 2008 /Pharmacology and Toxicology, "Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches", enclosed herewith as Annex 3.

D. As a result of these guidances, the identification limits provided in the ICH-Q3A may not be acceptable for genotoxic impurities, therefore the manufacturer should strive to achieve the lowest levels of genotoxic impurities that are technically feasible and/or levels that convey no significant cancer risk.

E. In an abbreviated manner, the qualification threshold for each impurity present together with the API has to be less than 0.15%, otherwise, it is necessary to reduce it to at least this limit.

F. In case of impurities of a genotoxic nature (mutagenic or carcinogenic), the qualification threshold must be much lower, and it must be related with the daily doses taken by the patient. In the case of Ulipristal (also known as VA-2914) this qualification threshold is around 0.015% or less.

G. The identification threshold for each impurity present together with the API is of less than 0.10% (impurities in an amount of 0.10% or higher must be identified),

and the reporting threshold for each impurity is of less than 0.05% (impurities in an amount of 0.05% or higher must be reported).

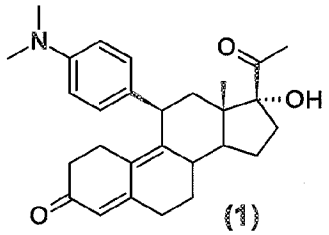
H. Only in very few cases, for example in the case that the impurity is the metabolite associated with the API or associated with studies such as: genotoxicity studies (point mutation, chromosomal aberration), general toxicity studies and others studies in relation with the safe of the patients, it is considered to accept levels higher than 0.15% for a specific impurity.

Concerning purification of VA-2914

VA-2914 obtained according to Kim

I. I have coordinated the analysis of VA-2914 obtained according to the process disclosed by WO 96/30390 by Kim ("Kim"), and the sample, having a total purity of 98.57% , has the following impurities [please see Exhibit 1]:

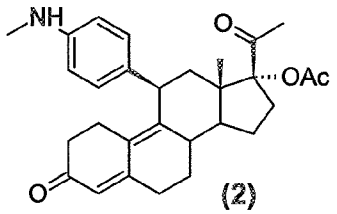
a) an associated impurity in an amount of **0.16%** at retention time of 4.870 corresponding with the compound 17-α-hidroxy-17β-acetyl-11β-((N,N'-dimethyl-4'-amino)phenyl)-19-norandrosta-4,9-diene-3-one (1)



(1)

so, this impurity must be reduced to less than 0.15% following the ICH Q3A guidance;

b) an associated impurity in an amount of 0.97% at retention time of 5.307 corresponding with 17-α-acetoxy-17β-acetyl-11β-((N-methyl-4'-amino) phenyl)-19-norandrosta-4,9-diene-3-one (2)



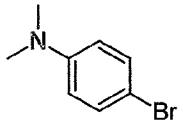
(2)

this impurity corresponds with the metabolite of VA-2914 and can be at levels of more than 0.15%, however, a lower amount of this impurity should be desirable;

c) an associated impurity in an amount of 0.06% at retention time of 6.294 (3); according to ICH-Q3A, it is not necessary to identify this impurity;

d) an associated impurity in an amount of 0.08% at retention time of 6.812 (4); according to ICH-Q3A, it is not necessary to identify this impurity;

e) an associated impurity in an amount of 0.11% at retention time of 10.599 corresponding with the compound p-bromo-dimethylaniline (6)



(6)

this impurity corresponds with a compound which is a potentially genotoxic impurity according with its structure since dimethylanilines are potential genotoxics [please see Delaney E.J., "An impact analysis of the application of the threshold of toxicological concept to pharmaceuticals", Regulatory

Toxicology and Pharmacology, 49, pp. 107-124, 2007, enclosed herewith as Annex 4; and Joseph R. Votano, et al., "Three new consensus QSAR models for the prediction of Ames genotoxicity", Mutagenesis vol. 19 no. 5 pp. 365-377, 2004, enclosed herewith as Annex 5]; consequently, the amount level of said impurity [compound (6)] must be of less than 0.015%. In addition, this impurity is very different structurally from VA-2914 and, therefore, this kind of impurities should be avoided.

J. The rest of peaks, except the peak corresponding with the API (VA-2914) [peak (5) retention time: 7.244], showed in the chromatogram, have amount levels of less than 0.05%, therefore, following the ICH-Q3A guidance, it is not necessary to report them [i.e., peak (7)].

VA-2914 obtained according to US 10/542,821

K. I have coordinated the analysis of VA-2914 obtained according to the process disclosed by US 10/542,821, and the sample, having a total purity of 99,20% , has the following impurities [please see Exhibit 2].

a) an associated impurity in an amount of 0.69% at retention time of 5.458 associated with the impurity (2) corresponding with the metabolite of VA-2914; thus, in this case, the amount of this impurity is significantly lower than the obtained following the process disclosed by Kim;

b) the rest of peaks, except the peak corresponding with the API (VA-2914) [retention time 7.51] showed in the chromatogram, have amount levels of less than 0.05%, therefore, according to ICH-Q3A, it is not necessary to identify said impurities.

CONCLUSION

L. The quality of the purified product (VA-2914) following the process disclosed by the applicants of US patent application No. 10/542,821 or following the process disclosed by Kim is very different in response to the pharmaceutical requirements:

- the VA-2914 compound purified following the process disclosed by Kim contain **five impurities in an amount of more than 0.05% each one**, wherein:

  ✓ impurity (1) has levels of more than 0.15% and does not fulfil the ICH-Q3A guidance;

  ✓ impurity (6) is a compound of potential genotoxic nature and appears at levels much higher than 0.015%, therefore it does not fulfil the EMEA and FDA guidances in relation with genotoxic impurities;

  ✓ metabolite (2), even known and not problematic, is in a level close to 1%; however, this level of impurity is not desirable following the ICH-Q3A guidance; and

  ✓ consequently, the VA-2914 compound purified according to the process disclosed by Kim has not the quality needed and it is not acceptable for commercial purposes; and

- the VA-2914 compound purified following the process disclosed by US patent application No. 10/542,821 **has only one impurity** of more than 0.05%, said impurity corresponding to the VA-2914 metabolite and being present at a level close to 0.7%; and, consequently, in this case, the quality of the VA-2914 compound fulfils all the requirements of EMEA and FDA guidances and it is commercially acceptable.

7. THAT with respect to the statement *"Because VA-2914 have a medicinal use further purification would be prima facie obvious"* [FOA, page 4, second paragraph, lines 7-8], another purpose of this Declaration is to point out my experience in relation with additional purifications following the process disclosed by Kim:

A. In my experience, the VA-2914 sample having a purity of 98.57% (obtained according to the process disclosed by Kim), once recristallysed and isolated from diethyl ether, cannot be re-dissolved again in said solvent (even if a large amount of solvent is used) in order to make another purification by the solution-precipitation approach.

B. The only possibility to purify it again in diethyl ether as solvent is by re-suspension and, under these conditions, the quality of the VA-2914 compound is almost the same.

C. In case of a further recrystallization using another solvent, for instance, ethanol or ethanol/water, the impurity profile is similar. **Besides, the colored impurities, which correspond to the potential genotoxyc p-bromo-dimethylaniline, remain in the final VA-2914 compound.**

D. Effectively, the white crystals obtained by the purification process disclosed by US patent application No. 10/542,821, by means of the hemisolvate obtained in the recrystallisation with isopropanol, followed by a filtration step, **it is related to the loss of the impurities associated with aniline derivatives, as for example, p-bromo-dimethylaniline** or so on, all of them being potentially genotoxic (Annexes 4 and 5).

E. Thus, in this case, "white crystals" mean "free of dimethyl aniline derivatives" such us p-bromo-dimethylaniline, the anilines being a group of compounds used as colorants or pigments in the industry. Although aniline itself is colorless, it slowly oxidizes and resinifies in air, giving a red-brown tint to aged samples.

8. THAT with respect to the statement *"(b) a melting point of "around" 189ºC would fall within the range of 183-185ºC taught by Cook"* [FOA, page 4, second paragraph, lines 4-5], another purpose of this Declaration is to discuss on the reliability of the differential scanning calorimetry technique for measuring the melting point of a compound. In this sense:

A. Differential scanning calorimetry (DSC) is a thermoanalytical technique that allows the measure of the melting point of a molecule with a very high precision. The basic principle underlying this technique is that, when the sample undergoes a physical transformation, for example, as a solid sample melts to a liquid, it will require more heat flowing to the sample to increase its temperature at the same rate as the reference. This is due to the absorption of heat by the sample as it undergoes the endothermic phase transition from solid to liquid.

B. The result of a DSC experiment is a curve of heat flux versus temperature or versus time, wherein the top of this curve represents the melting point with a very high precision.

C. Therefore, it is possible to differentiate without any doubt, between melting points of 183-185ºC mentioned for the product obtained according to the process disclosed by WO 99/45022 by Cook et al. ("Cook") and the melting point of 189ºC mentioned for the product purified according to the process disclosed by US 10/542,821.

D. As it is known, the melting point is an indicative key to measure the purity of a compound; in fact, when the melting point is higher, the purity also increases, what is a very simple form to prove it.

As a below-named declarant, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements,

and the like, so made are punishable by fine or imprisonment, or both, under Section 1001 or Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 02 - VIII - 2010

Antonio Lorente Bonde-Larsen

Enclosed:

Exhibit 1: Chromatogram of a VA-2914 sample obtained according to the process disclosed by Kim

Exhibit 2: Chromatogram of a VA-2914 sample obtained according to the process disclosed by US 10/542,821

Annex 1: ICH HARMONISED TRIPARTITE GUIDELINE / Impurities in New Drug Substances /Q3A(R2)

Annex 2: European Medicines Agency EMEA/CHMP/QWP/251344/2006, Guideline on the Limits of Genotoxic Impurities

Annex 3: Department of Health and Human Services /Food and Drug Administration /Center for Drug Evaluation and Research (CDER) /December 2008 /Pharmacology and Toxicology, "Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches"

Annex 4: Delaney, E.J. "An impact analysis of the application of the threshold of toxicological concept to pharmaceuticals", Regulatory Toxicology and Pharmacology, 49, pp. 107-124, 2007.

Annex 5: Joseph R. Votano, Marc Parham, Lowell H. Hall, Lemont B. Kier, Scott Oloff, Alexander Tropsha, Qian Xie and Weida Tong K. "Three new consensus QSAR models for the prediction of Ames genotoxicity", Mutagenesis vol. 19 no. 5 pp. 365-377, 2004.